REMARKS

This paper is responsive to the Office Action mailed July 15, 2003. Claims 1-14, 18-23 and 25-27 remain in this application. Claims 15-17, and 24 have been cancelled. Claims 4, 6, 8-13, 19, 20, 25 and 26 have been amended. Claims 28-32 have been added, support for which may be found in the specification, for example, at Page 26, Lines 11-17. No new matter has been introduced into the claims. Reconsideration of the subject application in light of the amendments herein and the remarks that follow is respectfully requested.

The Pending Claims Distinctly Claim and Particularly Point Out the Subject Matter Which Applicants Regard as the Invention for Purposes of 35 U.S.C. § 112, Second Paragraph

The Examiner rejected Claim 1 under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner argues that ULTRALENTE is a trademark/trade name, and therefore does not identify or describe the goods associated with it. Applicants respectfully traverse this rejection.

First, the trademark ULTRALENTE was cancelled on December 29, 2000– nearly three years ago. Therefore, Ultralente is no longer a trademark but rather refers to a specific type of long acting insulin. Applicants intentionally did not capitalize the word and defined "Ultralente-like crystals" in the specification at Page 24, Lines 28-32. Therefore, the meaning of Ultralente in this claim is clear and definite.

The Examiner also argues that the term "uni-modal" in Claim 1 is vague and indefinite. He states that the term is not described in the specification nor found in Merriam-Webster's Collegiate Dictionary. Applicants direct the Examiner's attention to the specification at Page 24, Lines10-15, wherein the term is defined as, "a distribution of particle sizes having a single region of abundant particle sizes accompanied, for the most part, by progressively fewer particles as the particle size increases or decreases from the abundant particle size region." Since Applicants have specifically defined this term, Applicants respectfully request that this rejection be withdrawn.

The Pending Claims are Fully Enabled for Purposes of 35 U.S.C. § 112, First Paragraph

The Examiner has rejected Claims 1, 3, 6, 7, and 23 for nonenablement of an insulin analog, a derivatized insulin, or a derivatized insulin analog.

The Examiner has not met his initial burden of establishing a reasonable basis on which to question enablement.

Under controlling Federal Circuit case law, it is axiomatic that a specification is presumed to be enabling unless the Examiner provides acceptable objective evidence or sound scientific reasoning showing that it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention. In *In re Cortright*, 49 USPQ2d 1464, 1466 (Fed. Cir. 1999), the court stated that the PTO cannot make a 112, first paragraph, rejection for lack of enablement, unless the PTO "has reason to doubt the objective truth of the statements contained in the written description." *See also, In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971) (A specification disclosure complies with th enablement requirement, "*unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.") Thus, under *Cortright* and *Marzocchi*, the claims in an application are presumed to be enabled unless proven otherwis .

Further, it is well-established that some experimentation is permitted, so long as it is not "undue." *See In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) ("Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation.") (footnotes omitted); *see also Ex parte Forman*, 230 USPQ2d 546, 547 (BPAI 1986) ("The ultimate question . . . is whether or not the specification contains a sufficiently explicit disclosure to enable one having ordinary skill in the relevant field to practice the invention claimed therein without the exercise of undue experimentation.").

In the present case, the Examiner has not provided any evidence or arguments addressing what information is missing and/or why a person of ordinary skill in the art could not practice the present invention without undue experimentation.

The Examiner states that there is no guidance or working examples for making crystals comprising the insulin analogs, derivatized insulins or derivatized insulin analogs of Claims 1, 3, 6, 7, and 23. Applicants respectfully disagree.

First, several insulin analogs are disclosed in the specification at Page 25, Line 6 to Page 26, Lin 10. Likewise, several derivatized insulins are disclos d in the

specification at Page 26, Line 11 to Page 29, Line 27. Applicants specifically teach how to make both insulin analogs and derivatized insulins at Page 30, Line 32 to Page 34, Line 5. Subsequently, Applicants specifically teach how to make crystals comprising these insulin analogs and derivatized insulins at Page 35, Line 1 to Page 37, Line 20. The term "protein solution" appears in the description for making these crystals (Page 35-37) as well as in Example 1 on Page 47, and at Page 34, Line 9-17, Applicants define the term "protein solution" to encompass insulin, insulin analogs, and derivatized insulins. Therefore, both the methods for making the crystals of the present invention described in the specification, and in a working example, encompass insulin analogs and derivatized insulins. Finally, Example 2 on Page 50 is a working example of using the crystals of the present invention *in vivo* to lower blood glucose levels, which is the goal of treating diabetes and hyperglycemia. Therefore, Applicants have enabled both how to make and use the crystals of the present invention and respectfully request that this rejection be withdrawn.

The Pending Claims Meet 35 U.S.C. § 103 Requirements

The Examiner rejected Claims 1-5 and 14 under §103 as being unpatentable over Hoffmann (US 5,534,488) in view of Schlichtkrull (US 2,819,999). The Examiner states that Hoffman teaches an insulin formulation for *parenteral administration* comprising a suspension of Ultralente crystals and a total formulation zinc concentration of between 0.5 mg to about 20 mg per 100 units of insulin. Schlichtkrull teaches a process for crystallization of insulin, resulting in *seed* crystals ranging in size from 1 micron to 7 microns. The Examiner concludes that it would have been obvious to one of ordinary skill to add the crystallization of insulin process of Schlichtkrull to the insulin formulation of Hoffmann because Hoffmann used previously prepared suspensions of Ultralente insulin crystals. Applicants respectfully traverse this rejection.

The United States Supreme Court has stated that to make out a case for obviousness, one must: "(1) determine the scope and content of the prior art; (2) ascertain the differences between the prior art and the claims in issue; (3) determine the level of skill in the pertinent art; and (4) evaluate any evidence of secondary considerations." *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). In addition, to support a *prima facie* case of obviousness over a combination of prior art references, th Examiner must establish that the prior art contains a suggestion or motivation to combine the prior art r f rences in such a way as to

achieve the claimed invention. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The Federal Circuit has also stated that hindsight is not a justifiable basis on which to find an invention obvious. *See In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999).

> Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field.

Id. at 999. Thus, to avoid hindsight analysis wherein the inventor's teachings are used against him/her, "there must be a rigorous application of the requirement for showing the teaching or motivation to combine the prior art references." *Id.* The Examiner's case must also include a finding that one of ordinary skill in the art at the time the invention was mad , would have reasonably expected the claimed invention to work. *See In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988). Further, it is inconsistent for the Examiner to argue that the references render the invention obvious while at the same time express doubt at the Applicants' ability to enable or show the usefulness of the claimed invention. *Hybridtech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

In this case, none of the cited references explicitly or implicitly teach, suggest or motivate a skilled person to combine the references and arrive at the invention without using Applicants' specification. The present invention provides crystals and pharmaceutical compositions of insulins that avoid incorporation of protamine, avoid incorporation of beef insulin, do not entail milling or grinding in their preparation, have a VMSED of 1 to about 5 microns with a uni-modal particle size distribution that are suitable for pulmonary administration and yet retain an extended time action of biological activity after administration.

The Hoffmann reference relates generally to a zinc fortified insulin formulation. Specifically, the reference teaches a suspension of Ultralente crystals and a total formulation zinc concentration of between 0.5 mg to about 20 mg per 100 units of insulin. Hoffmann teaches only subcutaneous administration of this formulation for the treatment of diabetes. The reference makes no suggestion whatsoever of a critical crystal size nor does it contemplate pulmonary administration. In the present invention, a small crystal size is critical for delivery by pulmonary administration. Schlichtkrull teaches a process for

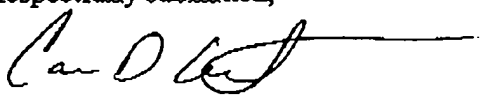
crystallization of insulin, with the resulting seed crystals ranging in size from 1 micron to 7 microns. These crystals are merely a seeding material that is used to make more crystals, and therefore, the reference does not teach anything about the crystal size of the end product. This reference does not mention anything about an insulin formulation comprising a specific crystal size necessary for pulmonary administration. Since neither one of these references contemplates pulmonary administration there is no way they could be combined to arrive at the present invention. Not only can one not arrive at the present invention by combining the above references, but also there is no indicia of a suggestion or motivation to combine the Schlichtkrull technique with the Hoffmann reference to arrive at the present invention. Therefore, Applicants respectfully request that this rejection be withdrawn.

The Examiner further rejected Claims 6-13, and 15-19 as unpatentable over Hoffmann in view of Schlichtkrull as applied to Claim 1 above and further in view of DeFelippis (US 5,952,297). Claims 15-17 have been cancelled. DeFelippis teaches only a seed suspension of human insulin, again for parenteral administration. As mentioned abov , there is no motivation to combine any of these references, and the addition of DeFelippis does not add anything that would render the present invention obvious. Applicants respectfully request that this rejection be withdrawn.

SUMMARY AND CONCLUSION

In view of the remarks and amendments enclosed and provided herein above, it is respectfully submitted that Examiner's rejections have been overcome. Applicants request reconsideration and withdrawal of the rejections. If Examiner feels that a telephone conversation with Applicants' attorney would be helpful in expediting prosecution of this case, the Examiner is invited to call Applicants' attorney.

Respectfully submitted,



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